REMARKS

Claims 1, 3-6, 9, 13, and 54-66 are currently pending. Claim 1 has been amended to recite alpha synuclein or an immunogenic fragment thereof, support for which is provided in dependent claims 3 and 4. Recital of "pharmaceutical" has been deleted as discussed in more detail below. Support for the amendment to claim 54 is provided at e.g., paragraph 156. Trademarks have been amended as suggested. No amendment should be construed as acquiescence in any ground of rejection. Lack of comment on any of the Examiner's remarks should not be construed as acquiescence therein.

Rejection under 35 USC 112, second paragraph

Claim 54 stands rejected based on the allegation that the term "good manufacturing conditions" is a relative term which renders the claim indefinite. The Examiner alleges that the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not reasonably be appraised of the scope of the claimed invention.

In reply, the term "good manufacturing practice" conditions was intended, and appropriate amendment has been made. "Good manufacturing practice" or GMP is a widely used and understood term of art that refers to the manufacturing practices required by the FDA or similar bodies in manufacturing pharmaceuticals. A quick search of Google reveals hundreds of thousands of hits for "good manufacturing practice." There are also several thousand hits for this term or its acronym GMP in the USPTO patent database. In view of the common usage and understanding of this term by those in the pharmaceutical industry, a skilled person would be reasonably apprised of the scope of the claimed invention.

Rejection of claims 1-6, 9-13, 54-55 under 35 USC 112, first paragraph

The Examiner states that although the specification is enabling for mere compositions comprising some immunogenic agents, it does not reasonably provide enablement for pharmaceutical compositions comprising all possible agents.

It appears from the Examiner's remarks on p. 7 of the office action that the use of the term "pharmaceutical" is being associated with an overly high standard of enablement, which requires evidence of not merely pharmaceutical activity but of clinical application. Nevertheless, this issue has been avoided by deleting the term "pharmaceutical" from the claims. The claims still require an adjuvant that is pharmaceutically acceptable for human administration. Thus, applicants' previous comments distinguishing the art remain equally relevant. Although the adjuvant must be suitable for administration to a human, the claims do not require that the compositions be administered to a human.

The claims have also been amended to define the agent as being alpha synuclein or an immunogenic fragment thereof.

MPEP 2164.03 describes the requirements for enablement of a composition claim:

> [W]hen a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

Based on the teaching of the specification, there would have been no difficulty in making any immunogenic fragment of alpha synuclein and combining it with an adjuvant suitable for administration to a human. Such fragments could be tested for pharmacological activity in transgenic mouse models as described in the specification. Even fragments lacking pharmacological activity would still be useful for generating antibodies as research reagents in which there is commercial market as evidenced by there being numerous commercial suppliers of such antibodies (see, e.g., attached product sheet from Santa Cruz Biotechnology).

Insofar as the Examiner's comments remain relevant to the pending claims, they will be addressed in turn.

At p. 4, the Examiner alleges that a fragment could be any dipeptide that is not necessarily unique to alpha-synuclein. In reply, the claims require that the fragment elicit an immune response to alpha-synuclein. It is unlikely that a two-amino peptide would be sufficient to generate an immune response to alpha synuclein. Moreover, even if a few immunogenic peptides from alpha synuclein did generate antibodies that cross-reacted with other proteins, such would not preclude their use either to produce a pharmacological activity or to generate antibodies against alpha synuclein.

The Examiner alleges that it is not clear how the working examples satisfy the recitation of a pharmaceutical composition. In reply, the working examples show inter alia that alpha-synuclein when administered with an adjuvant can induce a pharmacological response in a mouse model of synucleinopathic disease. Given this exemplification as a means of identifying a suitable fragment, the artisan can then turn to the general teaching of the specification for a selection of adjuvants suitable for use in humans to combine with such fragments.

The Examiner alleges that the data in Table 1 show no difference between the treated groups. In fact, there is a difference. The group with the highest titer had the smallest synuclein inclusions (range 10-22, mean 16), followed by the group with low titer (range 15-29, mean 22) followed by the controls, (range 18-29, mean 23.5). These data are consistent with there being a relationship between antibody titer and reduction of synuclein inclusions.

The Examiner further alleges that it is unpredictable from the art which immunogenic fragments would lead to a successful composition. In reply the specification provides evidence that at least fragments that induce antibodies to the NAC region and the C-terminus of alpha synuclein would lead to a successful pharmaceutical composition. The specification shows that an antibody to the NAC region induces clearing of amyloid deposits in an ex vivo assay. The ex vivo assay provides a means of screening antibodies for activity in treating Alzheimer's disease in which NAC is one component of amyloid plaques. The specification also provides evidence that results in this assay correlate with results in a transgenic animal model. The specification also shows that an antibody to the C-terminus of alpha

synuclein is able to reduce levels of membrane bound alpha synuclein in a cell-based assay. Postfiling evidence has shown that C-terminal antibodies and N-terminal antibodies also have pharmacological activity in a transgenic animal model of synucleinopathic disease (see examples 9-11 of commonly owned USSN 12/037,081). Fragments from other regions of alpha synuclein can be tested using the cell-based and transgenic animal models described in the specification.

The Examiner questions the removal of membrane bound alpha-synuclein in Example 2 in view of the description in the specification that Lewy bodies are intracellular in nature. In reply, alpha synuclein exists in both membrane bound and cytoplasmic forms within a cell. The membrane-bound form has been proposed to seed formation of Lewy bodies within the cytoplasm in a manner anal ogous to Abeta42 seeding formation of amyloid deposits (see, e.g., Lee et al., J. Biol. Chem., Vol. 277, Issue 1, 671-678, January 4, 2002). Thus, removal of membrane bound alpha-synuclein is an indication of pharmacological activity.

The Examiner cites post-filing comments by the present inventors and others that much work is required before clinical application as evidence of non-enablement. However, the average time between first discovery of a drug and marketing approval is thirteen years. Of necessity, most patent applications on drugs and method of treatment are filed early in the process before any public disclosure has occurred. The requirements under the law for obtaining a patent are not as stringent as the requirements for obtaining government approval to market a particular drug for human consumption. *In re Brana*, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). "Testing for full safety and effectiveness. . .is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." *Id.* Thus, the mention of further development before a treatment is available is not inconsistent with enablement.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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